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(54) Title: QUINAZOLINYL-AMINO DERIVATIVES HAVING α-ANTAGONIST ACTIVITY

(57) Abstract

New quinazolinyl-amino derivatives useful as α_1-adrenoreceptors blockers are described. These compounds can be used as therapeutical agents for treating affections and diseases related with the hyperactivity of the α-adrenergic system, as, for example, arterial hypertension, prostate benign hyperplasia (BHP), high intraocular pressure and hypercholesterolemia. Processes for the preparation of the above said compounds are also described.

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QUINAZOLINYL-AMINO DERIVATIVES HAVING α-ANTAGONIST ACTIVITY

The present invention refers to new derivatives of 4-amino-6,7-dimethoxyquinazoline having α-antagonist activity, their isomeric mixtures, the enantiomers, their addition salts with pharmaceutically acceptable acids or the pharmaceutical compositions containing them.

Among the quinazoline derivatives already known, in particular those comprising in their structure the piperazine-group, many present an antihypertensive or hypotensive activity both systemic and intraocular, and also a regulating activity on the biosynthesis of cholesterole.

For example US-3,511,836 describes quinazoline-derivatives having anti-hypertensive action. In particular among the described compounds the 1-(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-(2-furanylcarbonyl)piperazine (Prasozine) is actually used for this kind of therapy.

In US-4,026,894 other compounds structurally related to the above said are described, among them the 1(4-amino-6,7-dimethoxy-2-quinazolinyl)-4-[(tetrahydro-2-furanyl)-carbonyl]piperazine (Terazosine) is used as hypotensive agent and in the therapy of prostate benign hyperplasia (BPH).

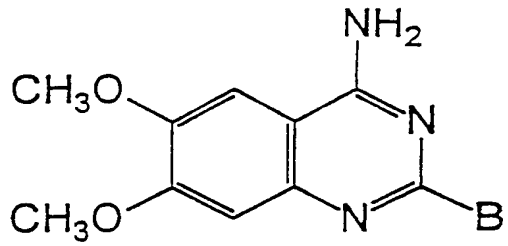
However, in the therapeutical treatment with the above said compounds, some undesired side effects where observed, such as: cephalea, somnolence, asthenia, nausea, palpitation. In some cases also postural effects were observed in conjunction with the usual symptoms associated with the decreasing of pressure, i.e. vertigo and light-headed.

It is therefore still desired to develop substances which, although therapeutically active against the above said disorders, show less marked side effects.

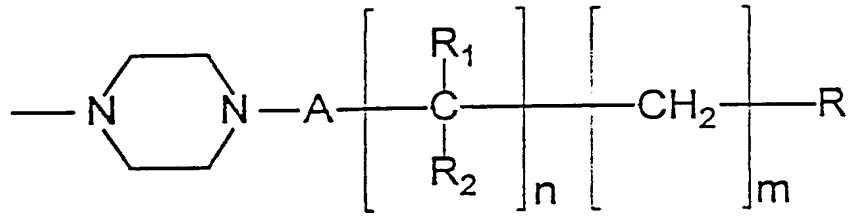
It was now founded, and it is an object of the present invention, that

modifying the substituents of the piperazine-ring new derivatives are obtained showing a good affinity for the α_1-adrenoreceptors and lower toxicity when compared with the known compounds.

The compounds according to the present invention have general formula (I)

(I) 

wherein B represent one of the following groups:

(B1) 

wherein:

A is chosen in the group of: a chemical bond, -CO-, -CONH-, each of them being represented in order to show that the left side is the part linked to the hetorocyclic ring and the right side is linked to the alkyl-chain;

R_1 and R_2, same or different, represent independently from each other an hydrogen atom, linear or branched alkyl- group having from 1 to 4 carbon atoms;

n is 0 or 1;

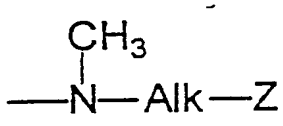
m is comprised between 0 and 4 and

R represents a group: aryl, diarylmethyl, aroyl, aryl(hydroxy)methyl, alkyloxycarbonyl, aryloxy unsubstituted or possibly substituted with one or more of the groups: alcoxy, branched or linear alkyl having from 1 to

4 carbon atoms, $-CONHR_3$ or $-N(R_4)R_5$ wherein:

R_3 is H, linear or branched alkyl having from 1 to 4 carbon atoms, aryl;

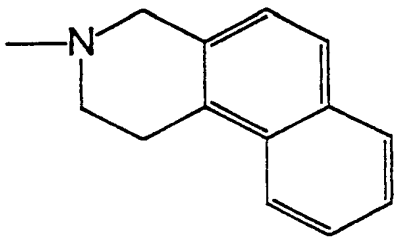
R_4 and R_5, same or different, represent independently from each other: H, linear or branched alkyl having from 1 to 4 carbon atoms, benzyloxycarbonyl, methanesulfonyl, benzyloxycarbonylglycinoyl;

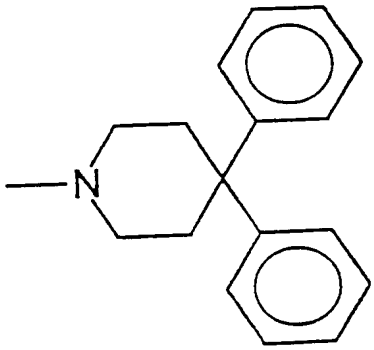
(B2) 

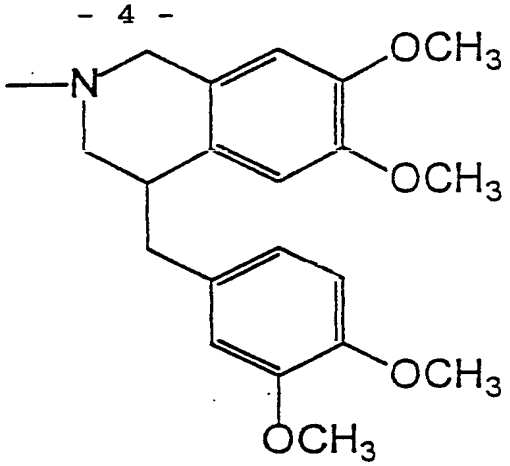
wherein

Alk represents alkyl having 1 to 3 carbon atoms and

Z is a phenyl, benzidryl or 4(2-methoxyphenyl)-1-piperazinyl;

(B3) 

(B4) 

(B5) 

The inventions includes also the enantiomers, the diastereoisomers, N-oxydes and the addition salts of these compounds with pharmaceutically acceptable acids.

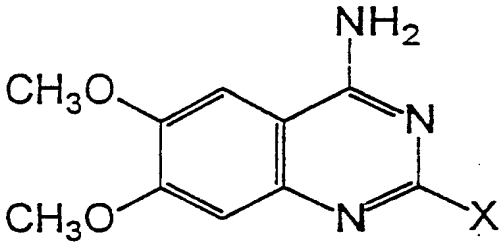
The compounds of the invention were tested in order to show their interest as substances having a potentially therapeutic activity. In particular the antagonistic activity on α_1-adrenoreceptors was determined and it was proved that the activity is present both "in vivo" and "in vitro". The toxicity-tests suggested a minor presence of undesired side effects.

Moreover, for some compounds according to the invention a good selectivity for the subline α_{1B}-adrenergic in respect of the sublines α_{1A} and α_{1D}.

The above reported results confirm the potential use of such compounds in the treatment of disorders related to an hyperactivity of the α-adrenergic system as, for example arterial hypertension, prostate benign hyperplasia, hugh intraocular pressure and hypercholesterolemia.

Synthesis of the compounds according to the invention

Generally the compounds of formula I can be prepared by condensing 2-haloquinazoline of formula II:



(II)

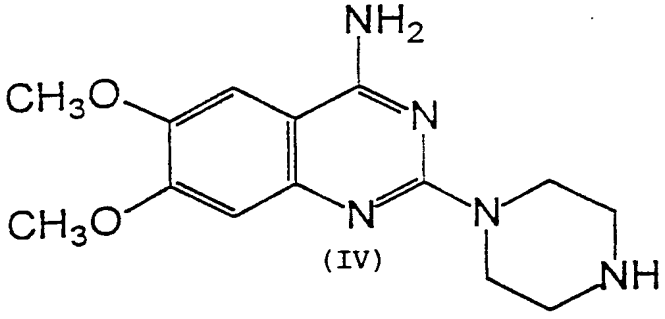
wherein X is an halogen atom, with amino-derivatives of formula III:

BH (III)

wherein B is anyone of the above said groups B_1 - B_5 as above defined excluded the case of B_1 when R is the group $-N(R_4)R_5$ wherein R_4 and R_5 are, both or independently, H or alkyl.

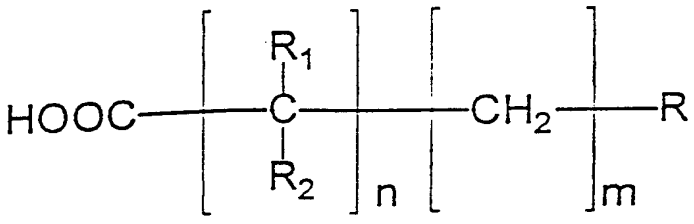
The above said condensation can be performed in polar solvents having high boiling point (for example isoamylalcohol, DMF) at 120°C/under reflux as shown in Examples 1, 2, 21, 22 and 28-33.

The compounds wherein B represents the group B_1 can also be prepared by condensation of the quinazoline-derivative of formula IV:



(IV)

with carboxylic acids of formula V:

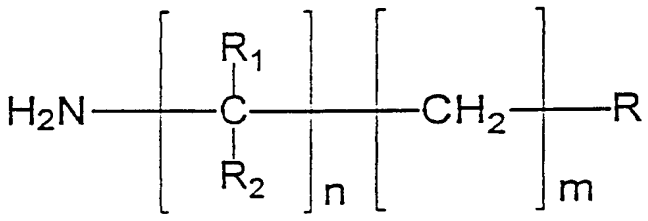


(V)

wherein R, R_1, R_2, n and m are as above defined or with reactive derivatives of such acids as for example the corresponding chlorides.

The above said condensations are performed in the presence of a condensing agent (for example N,N'-dicyclohexylcarbodiimide) and a promoting agent (for example 4-dimethylaminopyridine) in an aprotic and/or chlorinated solvent (for example DMF, $CHCl_3$) at 0°/+140°C as shown in the Examples 3-6, 11-13, 15, 17, 18 and 23-27. When reactive derivatives of the acids are used, the reactions are performed at 0°/+80°C in the presence of a tertiary-amine (for example triethylamine) or other acceptor of the formed acid.

Another method of preparation, shown in Example 10, is the reaction of the quinazoline derivative of formula IV with amines of formula VI:



(VI)

wherein R, R_1, R_2, n and m are as above defined, in the presence of N,N'-carbonyldiimidazole in an aprotic solvent (for example tetrahydrofuran) at 0°/+50°C.

The compounds wherein R represents an aryl(hydroxy)methyl-group can be prepared by reduction of the corresponding aroyl-derivatives with reducing agents (for example sodium borohydrure) in protic solvents (for example water or methanole) at 0°/+40°C (Examples 14 and 16).

The compounds wherein R is a $-N(R_4)R_5$ group, wherein R_4 and R_5 are H respectively, can be prepared by hydrolisys of the corresponding

compounds wherein R_4 or R_5 are the group $COOCH_2C_6H_5$.

Such reactions, shown in the Examples 7 or 8, are performed in protic solvents (for example acetic acid) in the presence of a strong acid (for example bromidric acid) at 0°/+40°C as described by T.W. Greene, Protective Groups in Organic Synthesis, p. 335, Wiley Interscience (1991) or according to other methods therein described.

The compounds wherein R is a group $-N(R_4)R_5$, wherein R_4 and R_5 are respectively H and a methanesulfonyl group, can be prepared by acylation with methanesulfonylchloride of the corresponding compounds wherein R_4 = R_5 = H. The reaction (Example 9) is performed in aprotic solvents (for example pyridine) in the presence of a base (for example triethylamine) at 0°/+40°C.

Detailed preparation of the intermediates

1-(2-Phenoxy-2-methylpropionyl)piperazine hydrochloride

(Intermediate I)

To a solution of 17.2 g of anhydrous piperazine in 50 ml of EtOH 95% and 22 ml of H_2O, 3.37 g of HBr 48% are dropped in about 10' and thereafter, in about 40' and at room temperature, a solution of 9.93 g of 2-phenoxy-2-methylpropionyl chloride (prepared according to: Bull. Soc. Chim. Fr. 1956, 776-783) in 70 ml of THF. The suspension is stirred 2 h at the same temperature and 3 h under reflux, diluted with 130 ml of THF, cooled, and the piperazine salts precipitated are filtered away. The filtered is evaporated to dryness, the residue is resuspended with 120 ml of H_2O and 35 ml HCl 2N and extracted with Et_2O; the aqueous phase is treated with 40 ml NaOH conc. and extracted with Et_2O (4x50 ml). The ethere-phase, dried, is treated with HCl in Et_2O about 3N and the precipitate is collected by filtration and crystallized from EtOH giving 5.98 g (42%) of

the wanted compound; m.p.: 236-238°C.

1-[2-Methyl-2-(2-methoxyphenoxy)propionyl]piperazine hydrochloride hydrated

(Intermediate II)

To a boiling solution of 10.5 g of 2-(2-methoxy-phenoxy)-2-methylpropionic acid, prepared according to: Gazz. Chim. It. 93, 335-338 (1963), in 50 ml of anhydrous $CHCl_3$ a solution of 5.4 ml of $SOCl_2$ in 20 ml of anhydrous $CHCl_3$ is dropped in about 30' and the solution is refluxed for 2 h. The residue obtained by evaporation to dryness of the solvent is used, instead of 2-phenoxy-2-methyl-propionyl chloride, to prepare the wanted compounds according to the method described for the Intermediate I. After crystallization from methyl-ethylchetone 6.3 g (34%) of Intermediate II are obtained; m.p. 95°-98°C.

2-Methoxy-6-isopropylphenoxyacetic acid

Intermediate III

To a mixture of: 20 g of NaOh in drops, 30 ml H_2O, 1.1 g triethylbenzylammonium chloride, 8.4 g 2-isopropyl-6-methoxyphenole (prepared according to: Tetr. Lett. 38, 1397-1404 (1982)) and 40 ml toluene, a solution of 11.1 ml of ethyle bromoacetate in 10 ml toluene is dropped at room temperature in about 15'. The mixture is stirred vigorously at the same temperature for 2 h and therefater for 2 h at 60°-65°C and for 6.5 h under reflux, during this last step a solution of 6 ml of ethyle broacetate in 10 ml of toluene is added. At the end the mixture is diluted with 250 ml H_2O, the aqueous phase is separated and treated with HCl conc.; the emulsified precipitate is extracted with Et_2O (3x50 ml) and the organic phase is washed with water. Another extraction is performed with 40 ml Na_2CO_3 at 20% or the slightly alcaline solution is

treated with HCl conc. and extracted with Et_2O (3x40 ml). The ether extracts are pooled and the solvent is evaporated giving 8 g (72%) of the wanted compound; b.p.: 190°C/0.7 mmHg.

2-(2-methoxy-6-isopropylphenoxy)propionic acid.

(Intermediate IV)

This compound is prepared as described according to the method given for Intermediate III but using ethyle 2-bromopropionate instead of ethyle bromoacetate. The wanted compound is isolated (yield 81%) and b.p.: 165-170°C/0.7 mmHg.

Detailed preparation of the final compounds

EXAMPLE 1

4-Amino-6,7-dimethoxy-2-(4-benzyl-1-piperazinyl)-quinazoline bihydrochloride hemihydrate

A mixture of 4.8 g of 4-amino-2-chloro-6,7-dimethoxyquinazoline (prepared according to: J. Med. Chem. 20, 146-149 (1977)) and 4.2 g of N-benzylpiperazine 95% in 120 ml of isoamylic alcohol is stirred under reflux for 4 h and therefater cooled. The precipitate is collected by filtration and suspended in 150 ml of water and 150 ml $CHCl_3$ and the mixture is treated with NaOH 30%. The organic phase is separated while the aqueous phase is once more extracted with $CHCl_3$ (2x50 ml); the organic extracts are pooled, washed with H_2O (2x30 ml), dryed on anhydrous Na_2SO_4 and the solvent is eliminated. The residue is purified by flash-chromatography on SiO_2 column eluting with $CHCl_3$/MeOH 100:3 and the fractions containing the pure base are pooled and evaporated to dryness. The residue is dissolved in EtOH and the solution treated with HCl 4N in EtOH up to complete precipitation of the salt which is collected by filtration and crystallized from MeCN/H_2O 7:3 giving 2.6 g

(56%) of the wanted compound; m.p.: 265-267°C.

EXAMPLE 2

4-Amino-6,7-dimethoxy-2-(4-diphenylmethyl-1-piperazinyl)-quinazoline bihydrochloride emihydrate

The compound is prepared according to Example 1, but using N-diphenylmethylpiperazine (prepared according to: J. Am. Chem. Soc. 71, 2731-2734 (1949)) instead of N-benzylpiperazine and warming under reflux for 8 h. The crude compound, collected by filtration, is crystallized from EtOH 95%, dissolved in MeOH, added with HCl dil. and the solution is evaporated to dryness. The residue is boiled with H_2O giving the wanted compound. Yield: 56%, m.p.: 273-274°C.

EXAMPLE 3

4-Amino-6,7-dimethoxy-2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-quinazoline hydrochloride . 0.75 H_2O

2.9 g of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)-quinazoline (prepared according to: J. Med. Chem. 20, 146-149 (1977)) are added in little portions, in about 10' and at room temperature, to a solution of 4.2 g dicyclohexylcarbodiimide 97% and 0.12 g of 4-dimethylaminopyridine in 60 ml $CHCl_3$. The mixture is stirred for 10' at the same temperature and added with 2.55 g of 2,2-diphenylacetic acid and again stirred for 6 h. The residue obtained after evaporation of the solvent is purified by flash chromatography on SiO_2 column eluting with $CHCl_3$/MeOH 100:2. The fractions containing the pure base are pooled, the solvents evaporated, the residue is dissolved in warm EtOH 95% and the solution treated with HCl in EtOH about 4N. The salt which crystallizes by cooling the solution is collected by filtration and recrystallized from EtOH 90% to give 3.2 g (60%) of the wanted compound; m.p.: 282 - 283°C.

EXAMPLE 4

4-Amino-6,7-dimethoxy-2-[4-(3,3-diphenylpropionyl)-1-piperazinyl]-quinazoline hydrochloride

Method a)

A solution of 7.92 g of 3,3-diphenylpropionic acid in 10 ml of anhydrous DMF is dropped, in about 15' and at room temperature, in a suspension of 5.8 g of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline, 8.42 g of cyclohexylcarbodiimide 97% and 0.37 g of 4-dimethylaminopiridine in 20 ml of anhydrous DMF. The clear olution so obtained is stirred at the same temperature for 5 h and a precipitated is formed (dicyclohexylurea) which is filtered away. The solvent is evaporated to dryness under vacuum and the resulting vetrous residue is filtered after treating with 500 ml Et_2O. The crude compound is purified by flash chromatography on SiO_2 column eluting with $CHCl_3$/MeOH 100:2. The fractions containing the pure base are pooled, the solvents evaporated to dryness, the residue suspended in warm EtOH and the suspension is treated with HCl in EtOH about 4N up to complete solution.

After cooling the crystallized salt is collected by filtration and recrystallized from MeCN/H_2O 8:2 giving 5.9 g (55%) of the wanted product; m.p.: 239-240°C.

Method b)

A solution of 4.4 g of 3,3-diphenylpropionyl chloride (prepared according: Coll. Czech. Chem. Commun. 25, 736-742 (1960) [CA 54, 13055h (1960)] in 30 ml of $CHCl_3$ free from EtOH is dropped at room temperature, in about 15', in a solution of 5.2 g of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)-quinazoline and 2.8 ml di Et_3N in 50 ml of anhydrous DMF.

The mixture is stirred at the same temperature for 6 h, the solvents

evaporated to dryness under vacuum, the residue dissolved in 150 ml $CHCl_3$ and the solution washed with $NaHCO_3$ 2.5% and H_2O and therefater dried on anhydrous Na_2SO_4. The process is continued as above described for method a) and 4.3 g (43%) of the wanted compound are obtained.

EXAMPLE 5

4-Amino-6,7-dimethoxy-2-{4-[(3-benzyloxycarbonylamino) propionyl]-1-piperazinyl}-quinazoline hydrochloride emihydrate

This compound is prepared according to Example 3 but 3-(benzyloxycarbonylamino)propionic acid is used instead of 2,2-diphenylacetic acid and stirring maintained for 5 h. The purification of the crude compound is performed by flash chromatography on SiO_2 column eluting with CH_2Cl_2/MeOH 100:5. The wanted compound is crystallized from EtOH 99%. Yield: 63%, m.p.: 166-168°C.

EXAMPLE 6

4-Amino-6,7-dimethoxy-2-{4-[(4-benzyloxycarbonylamino) butirryl]-1-piperazinyl}-quinazoline hydrochloride . 1.5 H_2O

This compound is prepared as described in Example 5, using 4-(benzyloxycarbonylamino)butirric acid instead of 3-(benzyloxycarbonylamino)propionic acid. The wanted compound is crystallized from EtOH and melts at 160-169°C. Yield 83%.

EXAMPLE 7

4-Amino-6,7-dimethoxy-2-[4-(3-aminopropionyl)-1-piperazinyl]-quinazoline dihydrobromide . 1.75 H_2O

20 ml of a solution of HBr 30% in AcOH is dropped, in about 10', in a solution of 4.95 g of the compound prepared in Example 5 in the form of base (prepared according to known methods) in 20 ml of AcOH. The mixture is stirred at the same temperature for 2 h and thereafter diluted with

800 ml Et_2O. The precipitate which is collected by filtration is crystallized from EtOH/H_2O 4.5:1 giving 4.7 g (85%) of the wanted compound; m.p.: 217°C.

EXAMPLE 8

4-Amino-6,7-dimethoxy-2-[4-(4-aminobutirryl)-1-piperazinyl]-quinazoline dihydrobromide . 0.25 H_2O

This compounds is prepared according to the Example 7 but using the compound prepared in Example 6 in the form of its base (prepared according to known methods). The crude compound is crystallized from MeOH and melts at 272-274°C. Yield: 84%.

EXAMPLE 9

4-Amino-6,7-dimethoxy-2-{4-[(4-methylsulfonylamino)butirry]-1-piperazinyl}-quinazoline hydrochloride

To a suspension of 5.3 g of the compound prepared in Example 8 in 50 ml anhydrous piridine 5.6 ml of Et_3N are dropped at room temperature and, after 15', 2 ml of methanesulfonylchloride are added at the same temperature and in about 10'. After 1 h stirring, the mixture is poured in 700 ml Et_2O and the precipitate, collected by filtration, is solved in 250 ml of H_2O and the solution added with sodium carbonate. The crude base is extracted with chloroform and the residue, obtained by evaporation of the solvent, is filtered after treatment with 250 ml Et_2O. The solid is purified by flash chromatography on SiO_2 column eluting in a CH_2Cl_2/MeOH gradient from 100:5 to 100:10. The fractions containing the pure base are pooled, the solvents evaporated and the residue suspended in warm EtOH 99%; the addition of HCl 4N in EtOH gives a clear solution from which, by cooling, the hydrochloride crystallizes. Another crystallization from EtOH 95% gives 2.1 g (43%) of the wanted

compound: m.p.: 231-233°C.

EXAMPLE 10

4-Amino-6,7-dimethoxy-2-{4-[(2-dimethylaminoethyl)amino-carbonyl]-1-piperazinyl}-quinazoline dihydrochloride tetrahydrate

To a suspension of 4.52 g of N,N'-carbonyldiimidazole in 30 ml anhydrous THF a solution of 2.48 g of N,N-dimethylethylendiamine 97% in 10 ml anhydrous THF is dropped and, after 15' stirring at room temperature, a solution of 5.8 g of 4-amino-6,7-dimethoxy-2-(1-piperazinyl)quinazoline in 250 ml anhydrous $CHCl_3$ is dropped therein in about 15'. The mixture is stirred at the same temperature for 24 h, added with 2.3 g of N,N'-carbonylimidazole and stirred for 48 h, thereafter the solvents are evaporated to dryness. The oily residue is purified by flash chromatography on SiO_2 column eluting with $CHCl_3/NH_3$ 3N in MeOH 100:10 and therefater on Al_2O_3 column eluting with $CHCl_3$/MeOH 100:10. The fractions containing the pure product are pooled, the solvents evaporated, the residue solved in EtOH and the solution treated with HCl 4N in EtOH. The solution is evaporated to dryness and the crude hydrochloride is crystallized from EtOH-AcOEt 2:1 to give 5.5 g (50%) of the wanted compound; m.p.: 206-210°C.

EXAMPLE 11

4-Amino-6,7-dimethoxy-2-{4-[2-(benzyloxycarbonylamino)-acetyl]-1-piperazinyl}-quinazoline hydrochloride

This compound is prepared as described in Example 5 but using N-benzyloxycarbonylglycine instead of 3-(benzyloxycarbonylamino)propionic acid and stirring the mixture for 7 h.

The purification of the crude compound is made by flash chromatography on SiO_2 column eluting with a mixture of $CHCl_3$/MeOH 100:3. The wanted

compound is crystallized from EtOH/H_2O 2:1. Yield: 79%; m.p.: 263-265°C.

EXAMPLE 12

4-Amino-6,7-dimethoxy-2-{4-[2-[2-(benzyloxycarbonylamino)-acetyl-amino]acetyl]-1-piperazinyl}-quinazoline hydrochloride hemihydrate

This compound is prepared according to Example 5 but using N-benzyloxycarbonylaminoacetylglycine instead of 3-(benzyloxycarbonylamino)propionic acid and DMF as reaction solvent. The crude compound is purified by flash chromatography on SiO_2 column eluting with a mixture of $CHCl_3$/MeOH 100:5. The wanted compound is crystallized from EtOH/H_2O 2:1. Yield: 60%; m.p.: 246-248°C.

EXAMPLE 13

4-Amino-6,7-dimethoxy-2-[4-(2-benzoylacetyl)-1-piperazinyl]-quinazoline

This compound is prepared according to Example 5 but using benzoylacetic acid instead of 3-(benzyloxycarbonylamino)propionic acid. The crude compound is purified by flash chromatography on SiO_2 column eluting with a mixture of CH_2Cl_2/MeOH 100:3. The wanted compound is crystallized from CH_3CN. Yield: 60%; m.p.: 214-215°C.

EXAMPLE 14

4-Amino-6,7-dimethoxy-2-[4-(3-hydroxy-3-phenylpropionyl)-1-piperazinyl]-quinazoline

To a suspension of 3 g of the compound prepared in Example 13 in 50 ml MeOH a solution of 0.43 g of $NaBH_4$ 96% in 4 ml iced H_2O containing 0.2 ml NaOH 30% is quickly added and the mixture is stirred at room temperature for 8 h. Thereafter 2 g (5x0.4) of $NaBH_4$ are added in 8 h. The suspension is diluted with 10 ml acetone, treated with diluted HCl, neutralized with sodium bicarbonate in 5% solution and concentrated under vacuum. The aqueous suspension is diluted with H_2O and extracted with $CHCl_3$; the

organic phase is washed with H_2O, dried on anhydrous Na_2SO_4 and the residue, obtained by evaporation of the solvent, is purified by flash chromatography on SiO_2 column eluting with CH_2Cl_2/MeOH 100:5. The crude compound, obtained after pooling the pure fractions and evaporating the solvent, is crystallized from EtOH giving 2.34 g (79%) of the wanted compound; m.p.: 222°C.

EXAMPLE 15

4-Amino-6,7-dimethoxy-2-{4-[(3-benzoyl)propionyl]-1-piperazinyl}-quinazoline hydrochloride hydrate

This compound is prepared according to Example 5 but 3-benzoylpropionic acid is used instead of 3-(benzyloxycarbonylamino)propionic acid. The crude product is purified by flash chromatography on SiO_2 column eluting with $CHCl_3$/MeOH 100:3. The wanted compound is crystallized from CH_3CN/H_2O 63:35 and melts at a temperature > 270°C. Yield: 62%.

EXAMPLE 16

4-Amino-6,7-dimethoxy-2-[4-(4-phenyl-4-hydroxybutirryl)-1-piperazinyl]-quinazoline maleate (1:1)

This compound is prepared according to Example 14 but the compound prepared in Example 15 is used instead of the one prepared in Example 13. The crude product is purified eluting the column with CH_2Cl_2/MeOH 100:10. The wanted compound is obtained with a yield of 67% after crystallization from EtOH; m.p.: 204-206°C.

EXAMPLE 17

4-Amino-6,7-dimethoxy-2-[4-(3-oxo-3-aminopropionyl)-1-piperazinyl]-quinazoline hydrochloride hydrate

This compound is prepared as described in Example 5 but 3-oxo-3-aminopropionic acid is used instead of 3-

(benzyloxycarbonylamino)propionic acid and as reaction solvent the anhydrous mixture $CHCl_3$/DMF 6:4 is used. The mixture is stirred at room temperature for 96 h during which is added, in portion, with 2 equivalents of 3-oxo-3-aminopropionic acid and 2.5 equivalents of N,N'-dicyclohexylcarbodiimide. Purification of the crude product is performed by flash chromatography on SiO_2 column in CH_2Cl_2/MeOH gradient from 100:20 to 100:50. The wanted compound is crystallized from EtOH 88%. Yield: 23%; m.p.: 241-243°C.

EXAMPLE 18

4-Amino-6,7-dimethoxy-2-[4-(2-ethoxycarbonylacetyl)-1-piperazinyl]-quinazoline hydrochloride

This compound is prepared as described in Example 5 but monoethylester of malonic acid is used instead of 3-(benzyloxycarbonylamino)propionic acid and as reaction solvent, DMF instead of $CHCl_3$ is used for 3 h at room temperature. Purification of the crude product is performed by flash chromatography on SiO_2 column eluting with CH_2Cl_2/MeOH 100:3. The wanted compound is crystallized from EtOH 80%. Yield: 60%; m.p.: 249-250°C.

EXAMPLE 19

4-Amino-6,7-dimethoxy-2-[4-(3-n-butylamino-3-oxopropionyl)-1-piperazinyl]-quinazoline hydrochloride

A mixture of 4 g of the compound prepared in Example 18 and 30 ml of n-butylamine in 10 ml DMSO is warmed at 140°C for 20h in a closed flask. The solution is evaporated under vacuum, the oily residue is treated with 200 ml H_2O and extracted with $CHCl_3$ (3x50 ml). The vitrous residue, obtained by evaporating the organic phase, is dissolved in 40 ml EtOH 95%, the solution is added with 10 ml KOH 0.3 N and warmed to reflux for 30'. The residue obtained by evaporation of the solution is purified by

flash chromatography on SiO_2 column eluting with a $CHCl_3$/MeOH gradient from 100:3 to 100:10. The crude product, obtained by evaporating the fractions containing the pure compound, is dissolved in 75 ml EtOH, the solution acidified with HCl in EtOH 4N and the hydrochloride is collected by filtration, crystallized from EtOH 90% giving 2.5 g (53%) of the wanted compound; m.p.: 260-262°C.

EXAMPLE 20

4-Amino-6,7-dimethoxy-2-[4-(phenylaminocarbonylacetyl)-1-piperazinyl]-quinazoline hydrochloride hemihydrate

A mixture of 4 g of the compound obtained in Example 18 and 14 ml aniline in 6 ml DMF is warmed at 155°C for 5.5 h.

The obtained product is purified as described in Example 19 by eluting with $CHCl_3$/MeOH gradient from 100:3 to 100:4. The crude hydrochloride is crystallized from DMF/H_2O 1:1 to give 1.54 g (31%) of the wanted compound; m.p.: >270°C.

EXAMPLE 21

4-Amino-6,7-dimethoxy-2-[4-(2-phenoxy-2-methylpropionyl)-1-piperazinyl]-quinazoline hydrochloride . 1.5 H_2O

This compound is prepared according to Example 2 but the intemediate I is used instead of N-diphenylmethylpiperazine and reflux maintained for 3 h. The precipitate is filtered and crystallized from isopropanole to give the wanted compound. Yield 78%; m.p.: 264°C.

EXAMPLE 22

4-Amino-6,7-dimethoxy-2-{4-[2-(2-methoxyphenoxy)-2-methylpropionyl]-1-piperazinyl}-quinazoline hydrochloride

This compound is prepared as described in Example 1 but intermediate II is used instead of N-benzylpiperazine, refluxing for 5 h and using a

AcOEt/MeOH gradient from 100:0 to 100:10 as eluting mixture. The wanted compound is crystallized from EtOH 80%. Yield: 57%; m.p.: 288°C (dec.).

EXAMPLE 23

4-Amino-6,7-dimethoxy-2-[4-(2-methoxyphenoxyacetyl)-1-piperazinyl]-quinazoline hydrochloride

This compound is prepared as described in Example 3 but 2-methoxyphenoxyacetic acid is used instead of 2,2-diphenylacetic acid and stirring maintained for 5 h. The residue, obtained after column purification, is crystallized from dioxane, suspended in EtOH 85% and acified with HCl about 4N in EtOH. The hydrochloride, collected by filtration, is crystallized from H_2O/DMF 2:1 to give the wanted compound. Yield 61%; m.p.: 263-265°C.

EXAMPLE 24

4-Amino-6,7-dimethoxy-2-{4-[(2-methoxy-6-isopropylphenoxy)acetyl]-1-piperazinyl}-quinazoline hydrochloride

To a boiling solution of 6 g of intermediate III in 30 ml CCl_4 3.6 ml of $SOCl_2$ are dropped and the mixture is stirred under reflux for 2 h. The oily residue, obtained by evaporation of the reaction mixture, is reacted with 4-amino-6,7-dimethoxy-2-(1-piperazinil)quinazoline instead of 3,3-diphenylpropionyl chloride in order to obtain the wanted compound as described in Example 4 (Method b), stirring for 2 h. The purification is performed by column chromatography using $CHCl_3$/MeOH 100:3 as eluting mixture. The wanted compound is crystallized from EtOH. Yield: 45%; m.p.: 252-254°C.

EXAMPLE 25

4-Amino-6,7-dimethoxy-2-{4-[(2-isopropyl-5-methylphenoxy)acetyl]-1-piperazinyl}-quinazoline hydrochloride . 0.25 H_2O

This compound is prepared according to Example 5 but 2-isopropyl-5-methylphenoxyacetic acid (prepared according to: Cesk. Farm. 17, 28-33 (1968) [CA 69, 67041g (1968)]) is used instead of 2,2-diphenylacetic acid and stirring maintained for 5 h. The wanted compound is crystallized from EtOH 95%. Yield: 80%; m.p.: 251-253°C.

EXAMPLE 26

4-Amino-6,7-dimethoxy-2-{4-[2-(2-methoxy-6-isopropylphenoxy)propionyl]-1-piperazinyl}-quinazoline hydrochloride

To a boiling solution of 4.8 g of the intermediate IV in 25 ml CCl_4 3 ml of $SOCl_2$ are dropped in about 15' and the mixture is refluxed for 3 h. The oily residue, obtained by evaporating the rection mixture, is used instead of 3,3-diphenylpropionyl chloride, stirring for 2 h in order to obtain the wanted compound as described in Example 4 (Method b). The compound is purified as described in Example 25 and the wanted compound is crystallized from EtOH. Yield: 58%; m.p.: 227-229°C.

EXAMPLE 27

4-Amino-6,7-dimethoxy-2-[4-(2,6-dimethoxyphenoxy)acetyl-1-piperazinyl]-quinazoline hydrochloride . 0.25 H_2O

This compound is prepared according to Example 5 but 2,6-dimethoxyphenoxyacetic acid (prepared according to GB-679,676) is used instead of 2,2-diphenylacetic acid and using $CHCl_3$/MeOH 100:1 as column eluting mixture. The wanted compound is crystallized from EtOH 95% and thereafter from DMF. Yield: 21%; m.p.: 258-260°C (dec).

EXAMPLE 28

4-Amino-6,7-dimethoxy-2-(N-benzyl-N-methylamino)-quinazoline hydrochloride

This compound is prepared according to Example 1 but N-meyhylbenzylamine

is used instead of N-benzylpiperazine and reflux maintained for 7 h. The crude base is purified by crystallization from EtOH, then dissolved in boiling EtOH and the solution is added with HCl about 4N in EtOH. The wanted compound is obtained with a yield: 62%; m.p.: 261-262°C.

EXAMPLE 29

4-Amino-6,7-dimethoxy-2-(N-methyl-3,3-diphenylpropylamino)-quinazoline hydrochloride

This compound is obtained according to Example 1 but N-methyl-3,3-diphenylpropylamine (prepared according to DE-925,468) is used instead of N-benzylpiperazine and reflux maintained 12 h. The purification of the crude base is performed by flash chromatography on SiO_2 column using as eluents $CHCl_3$/MeOH 100:2. The wanted compound is crystallized from EtOH 95%. Yield 29%; m.p.: 258-259°C.

EXAMPLE 30

4-Amino-6,7-dimethoxy-2-(1,2,3,4-tetrahydrobenzo[f]isoquinolin-2-yl)-quinazoline . 0.25 ethanole

This compound is prepared according to Example 1 but using 1,2,3,4-tetrahydrobenzo[f]isoquinoline (prepared according to Indian J. Chem. 1974, 113-116) instead of N-benzylpiperazine and refluxing 9 h in the darkness and under nitrogen. The purification is performed by flash chromatography on SiO_2 column eluting with a CH_2Cl_2/NH_3-MeOH 5N gradient from 100:0.5 to 100:1.5. The wanted compound is crystallized from EtOH 99%. Yield: 30%; m.p.: 177-180°C (dec)

EXAMPLE 31

4-Amino-6,7-dimethoxy-2-{N-methyl-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl}amino}-quinazoline dihydrochloride dihydrate

This compound is prepared as described in Example 1 but using N-methyl-3-

[4-(2-methoxyphenyl)-1-piperazinyl]-propylamine (prepared according to DE-2,143,730) instead of N-benzylpiperazine and refluxing 12 h. The crude base is purified by flash chromatography on SiO_2 column eluting with $CHCl_3/NH_3$-MeOH about 2N 100:3. The wanted compound is crystallized from EtOH 92%. Yield: 60%; m.p.: 208-210°C.

EXAMPLE 32

4-Amino-6,7-dimethoxy-2-(4,4-diphenyl-1-piperidinyl)-quinazoline hydrochloride . 0.65 H_2O

This compound is prepared as described in Example 1 but 4,4-diphenylpiperidine [prepared according to Arzneim.-Forsch. 34, 233-240 (1984)] instead of N-benzylpiperazine and refluxing for 8 h. The crude base is purified by crystallization from DMF-H_2O (3:1). The wanted compound is crystallized from DMF-H_2O (1:1). Yield 61%; m.p.: > 290°C.

EXAMPLE 33

4-Amino-6,7-dimethoxy-2-[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]-quinazoline hydrochloride hydrate

A mixture of 3.6 g of 4-amino-2-chloro-6,7-dimethoxy-quinazoline, 5.15 g 1,2,3,4-tetrahydropapaverine (prepared according to Eur. J. Med. Chem. - Chim. Ther. 9, 233-238 (1974)), 2.16 g potassium iodide and 15 ml anhydrous DMF is warmed under stirring at 120-125°C for 8 h. The mixture is poured in 400 ml H_2O and the precipitate, collected by filtration, is purified by flash chromatography on SiO_2 column eluting with $CHCl_3$/MeOH 100:1 and the fractions containing the pure base are pooled and evaporated to dryness. The residue is dissolved in MeOH and the solution treated with HCl in Et_2O about 3 N up to complete precipitation of the salt which is filtered and crystallized from MeOH to give 6.31 g (70%) of the wanted compound; m.p.: 226-230°C.

PHARMACOLOGICAL DATA

Methodology

Male Sprague Dawley rats (Crl: CD' BR) of 175-300 g b.w., male spontaneously hypertensive rats, Okamoto strain, female Albino Swiss mice [Crl: CD-1 (ICR) BR] 20-30 g b.w., were obtained from Charles River, Italy. Animals were housed with free access to food and water and maintained on forced light-dark cycle at 22-24°C until the day of experiments.

Acute toxicity

The acute toxicity of synthesized compounds was evaluated in female Albino Swiss mice after intraperitoneal and oral administration. Four logarithmic scaled doses of the compounds were dissolved or suspended in 0.5% Methocel and administered in a volume of 10 ml/kg to groups of 4 mice/dose. Mortality was recorded 7 days after the administration. Data analysis: the LD_{50} values and their fiducial limits were calculated according to the method of Weil [Biometrics, 8, 249, 1952].

Receptor Binding studies

The following receptor binding studies, as well as the experimental data reported below, establish compounds of the invention as α_1-blockers.

[^{3}H]Prazosin binding (α_1-receptors)

Rat cerebral cortices were homogenized in 50 volumes of original wet weight of ice-cold 50 mM Tris-HCl buffer pH 7.4. The homogenates were centrifuged at 48,000 x g for 10 minutes, and the pellets were resuspended in the same volume of ice-cold buffer, centrifuged and resuspended two more times. The final pellets obtained were resuspended in 100 vols of 50 mM Tris-HCl buffer (containing 0.1% ascorbic acid and 10 µM pargyline) pH 7.4 and incubated (1 ml/sample) for 30 min at 25°C

with 0.35 nM [^{3}H]prazosin, in absence or presence of 5-10 concentrations of the displacing compound to be tested. Non specific binding was determined in the presence of 2 µM prazosin. The incubations were terminated by rapid filtration through Whatman GF/B, filters using a Brandel cell harvester and the filters were washed with 3x3 ml of ice-cold buffer. The radioactivity retained on the filters was determined by liquid scintillation counting.

Cloned animal α_1 adrenoceptors

Expression of rat brain α_{1D} (previously $\alpha_{1A/D}$), syrian hamster smooth muscle cell line DDT1 MF-2 1B and bovine brain α_{1A} (previously α_{1C}) adrenoceptors transiently in COS-7 cells (modified monkey kidney ephitelial cells) was performed as previously described [S. Cotecchia et al., Proc. Natl. Acad. Sci. USA 85, 7159, 1988; D.A. Schwinn et al., J. Biol. Chem. 265, 8183. 1990; J.W. Lomasney et al., J. Biol. Chem. 266, 6365, 1991]. COS-7 cells were grown as monolayers in Dulbecco's modified Eagle's medium (DMEM), supplemented with 25 mM glucose, 10% bovine calf serum, 100 units/ml penicillin and 100 µg/ml streptomicyn sulfate.

Transfected cells from colture flask were washed two times with 5 ml phosphate buffered saline (PBS), scraped into 2 ml of 5 mM Tris-HCl, pH 7.4, containing 5 mM EDTA and 10 µM leupeptin, and lysed by sonication. The cell lysates were pelleted at 30000xg for 15 min at 4°C and washed three times with 10 ml ice-cold 50 mM Tris-HCl, pH 7.4. Membranes were resuspended in 50 mM Tris-HCl, pH 7.4, containing 10 µM pargyline and 0.1% ascorbic acid, quickly frozen and stored at -70°C until utilized.

Radioligand binding assays

Membranes were incubated in 50 mM Tris-HCl, pH 7.4, containing 10 µM pargyline and 0.1% ascorbic acid, with 0.3-0.6 nM [^{3}H]prazosin in absence

or presence of the displacing drug to be tested over the concentration range 10^{-4} to 10^{-13} M. Incubation volume was 0.22 ml (35, 35 and 70 µg protein/sample for α_{1B}, α_{1A} and α_{1D}, respectively).

Non-specific binding was determined in presence of 100 µM phentolamine. The reaction mixture was incubated for 30 min at 25°C and then stopped by the addition of ice cold Tris-HCl buffer and rapid filtration through 0.2% polyethyleneimine pretreated Whatman GF/B fiber filters using Brandel cell harvester. The filters were then washed with 3x3 ml of ice-cold buffer and the radioactivity retained on the filters was counted in 10 ml of Filter Count (Packard) in a liquid scintillation spectrometer with a counting efficacy of 40%.

Data analysis

The inhibition of specific binding of the radioligands by the tested drugs was analyzed to estimate the IC_{50} value by using the non-linear curve-fitting program Allfit [A. De Lean et al., Am. J. Physiol. 235,

Evaluation of the antihypertensive activity in chateterized spontaneously hypertensive rat (SH) chronic awake and of the hypotensive activity in the normotensed anesthethized rat

The SH rats are surgically prepared at least 24 hours before the test. The surgical operation was performed under neuroleptoanalgesia or barbituric anesthesia; the right carotid artery was exposed and a chateter suitable in dimensions and material was introducted in the vessel up to the aortic arch. The chateter was linked to the vessel with suitable suture thread and run under the skin up to the animal neck where was brought to the exterior and connected to a "Swivel" which allows free-motion of the animal, inside its cage, during testing. The chateter end was connected to a pressure transductor which send the signal to

polygraph pre-amplifier.

For endovenous administrations a second chateter similar to the one above described was introduced during the surgical operation into the left jugular vein and brought to the exterior as the arterious chateter. Both chateters where filled with suitable volumes of eparinated solution, in order to prevent coaugulation or formation of thrombuses, which will prevent the registration of the pressure wave or the endovenously administration of the solution. About 30' before administration the arterious pressure was monitored and the registration of the parameters was performed after administration at different times according to the test protocol.

Normotensed rats with were prepared surgically at the moment of the test, after anesthesia with pentobarbital. Suitable chateters were introduced in the left carotid artery and the right jugular vein. The arterious chateter end was connected to a pressure transductor which sends the signal to a polygraph preamplifier. About 30' before the administration the arterious pressure was monitored and the registration of the parameters was performed after the administration, at various time according to the test protocol.

For the endovenous administration the administered volum was 0.5 - 1 ml/Kg, while for the oral administration was 5 ml/Kg.

Evaluation of data: in so far as the espression of the results is concerned, the pressure data were reported as percentage of the variation in respect to the base values. Based on these data, at the maximum of the effect, a DE_{25} was evaluated (as the dose which induces a lowering of 25% of the dyastolic arterious pressure) by linear regression log-dose against response.

For example the compound described in Example 13 shows a DE_{25} of 56 µg/Kg following to the endovenous administration in the normotensed rat and a DE_{25} of 2.42 mg/Kg after oral administration in SHR rat.

Results

The compounds prepared in the examples were tested according to the above reported methods and compared with the results obtained with the usual standards.

The results are reported:

- In TABLE 1 in connection with the affinity for the α_1([^{3}H]prazosine) receptor and their acute toxicity (DL_{50});
- in TABLE 2 in connection with the shown affinity for sublines of cloned receptors α_{1A}, α_{1B}, α_{1D}.

TABLE 1

Example No.	[^{3}H]prazosine IC_{50} nM	DL_{50} mg/kg	
		i.p.	p.o.
1	32	76	301
2	40	-	-
3	5	112	868
4	3	97	>3000
5	283	300	>3000
6	29	>1000	>3000
7	48	187	>3000
8	47	219	>3000
9	86	>500	-
10	55	23	1346
11	61	>1000	>3000
12	29	1132	>2000
13	7	142	>3000
14	19	>1000	>3000
15	15	>1000	>3000
16	17	253	>3000
17	105	-	-
18	54	>1000	>3000
19	96	459	>2000
20	67	-	-
21	99	206	>1700
22	49	435	>3000
23	17	337	>2000
24	28	268	>3000
25	157	346	>3000
26	123	115	1957
27	6	-	-
28	70	89	293
29	85	163	>2000
30	5	-	-
31	12	70	>2000
32	259	>500	>2000
33	287	884	>3000
prazosine	2	-	1852

TABLE 2

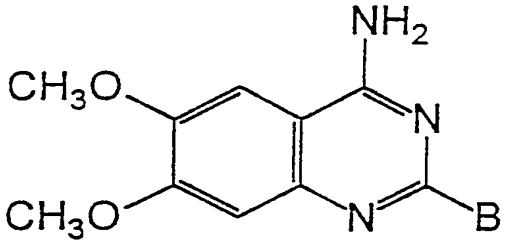
Affinity for the cloned α_1-adrenoceptor subtypes

Data represent the IC_{50} values (nM) and are the mean of 2-4 different experiments, each done in triplicate, which agreed within 10%.

compound	cloned α_{1A}	cloned α_{1B}	cloned α_{1D}
Example 24	17.17	1.15	22.93
Example 33	950.03	205.64	1549.23
Prazosin	3.04	2.27	5.08
Terazosin	66.63	71.95	105.63

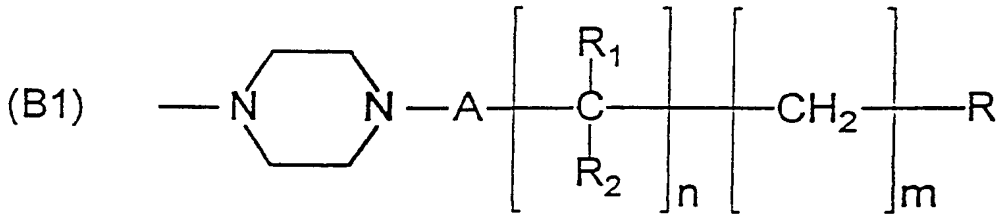
CLAIMS

1. Compound of general formula (I):



(I)

wherein B is one of the following groups:



wherein:

A is chosen in the group of: a chemical bond, -CO-, -CONH-, each of them being represented in order to show that the left side is the part linked to the hetocyclic ring and the right side is linked to the alkyl-chain;

R_1 and R_2, same or different, represent indepently from each other an hydrogen atom, linear or branched alkyl group having from 1 to 4 carbon atoms;

n is 0 or 1;

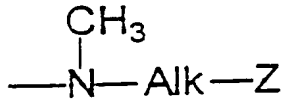
m is comprised between 0 and 4 and

R represents a group: aryl, diarylmethyl, aroyl, aryl(hydroxy)methyl, alkyloxycarbonyl, aryloxy unsubstituted or possibly substituted with one or more of the groups: alcoxy, branched or linear alkyl having from 1 to

4 carbon atoms, $-CONHR_3$ or $-N(R_4)R_5$ wherein:

R_3 is H, linear or branched alkyl having from 1 to 4 carbon atoms, aryl;

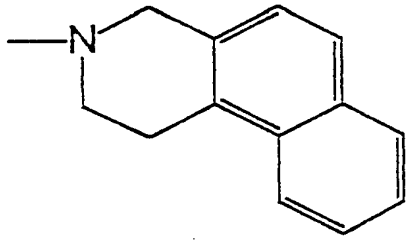
R_4 and R_5, same or different, represent independently from each other: H, linear or branched alkyl having from 1 to 4 carbon atoms, benzyloxycarbonyl, methanesulfonyl, benzyloxycarbonylglycinoyle;

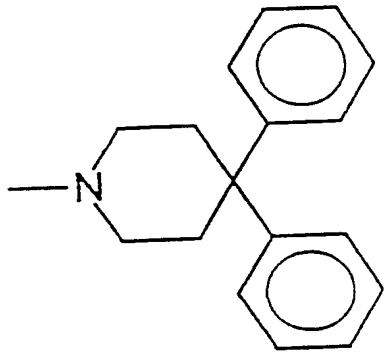
(B2) 

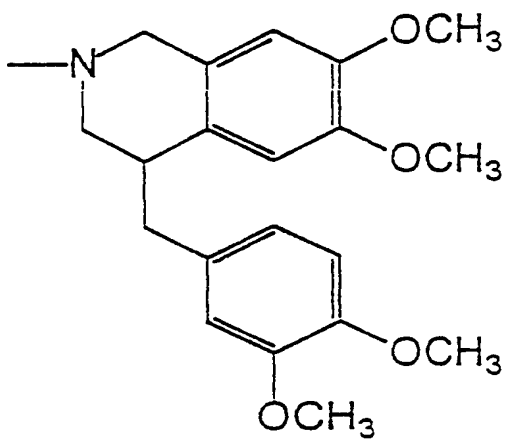
wherein

Alk represents alkyl having 1 to 3 carbon atoms and

Z is a phenyl, benzidryl or 4-(2-methoxyphenyl)-1-piperazinyl;

(B3) 

(B4) 

(B5) 

or an enantiomer, diastereoisomer, N-oxide, addition salt with a pharmaceutical acceptable acid thereof.

2. Compound, according to claim 1, represented by the formulae:

4-Amino-6,7-dimethoxy-2-(4-benzyl-1-piperazinyl)-quinazoline

4-Amino-6,7-dimethoxy-2-(4-diphenylmethyl-1-piperazinyl)-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(2,2-diphenylacetyl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(3,3-diphenylpropionyl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-{4-[(3-benzyloxycarbonylamino)propionyl]-1-piperazinyl}-quinazoline

4-Amino-6,7-dimethoxy-2-{4-[(4-benzyloxycarbonylamino)butirryl]-1-piperazinyl}-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(3-aminopropionyl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(4-aminobutirryl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-{4-[(4-methylsulfonylamino)butirryl]-1-piperazinyl}-quinazoline

4-Amino-6,7-dimethoxy-2-{4-[(2-dimethylaminoethyl)amino-carbonyl]-1-piperazinyl}-quinazoline

4-Amino-6,7-dimethoxy-2-{4-[2-(benzyloxycarbonylamino)acetyl]-1-piperazinyl}-quinazoline

4-Amino-6,7-dimethoxy-2-{4-[2-[2-(benzyloxycarbonylamino)-acetyl-amino]acetyl]-1-piperazinyl}-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(2-benzoylacetyl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(3-hydroxy-3-phenylpropionyl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-{4-[(3-benzoyl)propionyl]-1-piperazinyl}-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(4-phenyl-4-hydroxybutirryl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(3-oxo-3-aminopropioyl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(2-ethoxycarbonylacetyl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(3-n-butylamino-3-oxopropionyl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(phenylaminocarbonylacetyl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(2-phenoxy-2-methylpropionyl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-{4-[2-(2-methoxyphenoxy)-2-methylpropionyl]-1-piperazinyl}-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(2-methoxyphenoxyacetyl)-1-piperazinyl]-quinazoline

4-Amino-6,7-dimethoxy-2-{4-[(2-methoxy-6-isopropylphenoxy)acetyl]-1-piperazinyl}-quinazoline

4-Amino-6,7-dimethoxy-2-{4-[(2-isopropyl-5-methylphenoxy)acetyl]-1-piperazinyl}-quinazoline

4-Amino-6,7-dimethoxy-2-{4-[2-(2-methoxy-6-isopropylphenoxy)propionyl]-1-piperazinyl}-quinazoline

4-Amino-6,7-dimethoxy-2-[4-(2,6-dimethoxyphenoxy)acetyl-1-piperazinyl]}-quinazoline

4-Amino-6,7-dimethoxy-2-(N-benzyl-N-methylamino)-quinazoline

4-Amino-6,7-dimethoxy-2-(N-methyl-3,3-diphenylpropylamino)-quinazoline

4-Amino-6,7-dimethoxy-2-(1,2,3,4-tetrahydrobenzo[f]isoquinolin-2-yl)-quinazoline

4-Amino-6,7-dimethoxy-2-{N-methyl-N-{3-[4-(2-methoxyphenyl)-1-piperazinyl]propyl}amino}-quinazoline

4-Amino-6,7-dimethoxy-2-(4,4-diphenyl-1-piperidinyl)-quinazoline

4-Amino-6,7-dimethoxy-2-[1-(3,4-dimethoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolin-2-yl]-quinazoline

3. Pharmaceutical composition wherein the active principle is a compound according to claims 1 and 2 or an enantiomer, diastereoisomer, N-oxyde or pharmaceutically acceptable salts thereof, in combination with pharmaceutically acceptable excipients, eluents or carriers.

INTERNATIONAL SEARCH REPORT

Int. onal Application No
PCT/EP 95/01001

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D239/95 C07D401/04 A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP,A,0 225 866 (GEROT-PHARMAZEUTIKA.) 16 June 1987 see page 1 - page 5; claims	1-3
X	DE,A,34 19 223 (SPOFA) 6 December 1984 see page 7, line 18 - page 9; claims	1-3
X	EP,A,0 028 031 (MITSUBISHI) 6 May 1981 see paragraph 12 -paragraph 34; claims; example 9; table 4	1-3
X	US,A,4 062 844 (PH.D. HAMMEN) 13 December 1977 see claims; examples 4,13	1-3
X	US,A,3 511 836 (H.-J. HESS) 12 May 1970 cited in the application see claims; tables XXXIII,XXXV	1-3

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 July 1995	14. 07. 95

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+ 31-70) 340-3016	Francois, J

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INTERNATIONAL SEARCH REPORT

Intc ›nal Application No
PCT/EP 95/01001

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	US,A,5 110 927 (J.PITHA) 5 May 1992 see claims; examples 7,8,39; table 1	1-3
X	FR,A,2 389 614 (SYNTHELABO) 1 December 1978 see page 1 - page 8; claims; example 3	1-3
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